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Statement of Purpose:
AIDS Treatment News reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations that work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

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Weekend Treatment Interruptions for Certain Well-Controlled Patients: Interview with Cal Cohen, M.D.

by John S. James

Dr. Cal Cohen is the research director of the Community Research Initiative of New England, teaches at Harvard Medical School in Boston, and is affiliated with Harvard Vanguard Medical Associates. Dr. Cohen spoke with *AIDS Treatment News* on September 10, 2004. We published part I of the interview in issue #405.

AIDS Treatment News: Explain the short-cycle treatment interruptions being tested at the Community Research Initiative in Boston. Is this still research only, or something people might try?

Dr. Cohen: Over a year ago we decided to study what would happen when patients take antiretrovirals five days a week instead of seven days. The rationale was based partly on data presented four years ago at the Durban conference in South Africa. Doctors Mark Dybul and Tony Fauci were excited by their data on antiretrovirals taken seven days on followed by seven days off, in patients whose virus was very well suppressed when they started. It seemed to work with boosted indinavir; then Dybul tested a cohort of eight people on ddI plus 3TC plus efavirenz, and again had excellent response alternating seven days on and seven days off. Some of my patients wanted to try it because they wanted to have the week without pills, and it seemed to work for them.

But this regimen did not gain wide acceptance, and the field retreated from it after the Paris meeting in the summer of 2003, where we saw that Thai and European researchers tried seven days on and seven days off but found a fair amount of virologic failure. While it worked for some people, it did not work for all who were virologically well suppressed when they started. Clearly there were rules that had to be worked out.

We decided to try a next step. If 7 days off

was at least sometimes too long, what other ratios might be more appealing? Since about age 5, all of us have a schedule of five-two in our lives; we went to school five days a week and had weekends off, and usually in the workplace it was five to two as well.

As we started to explore, we found that even as far away as Botswana people have a five-day workweek and a two-day weekend. This ratio seems to be surprisingly common among several human cultures.

And the point of the "short-cycle" (or short periods of time off, versus "long cycle" meaning taking many weeks to months off) interruption was to improve adherence and make treatment easier -- to give people a break and also have it be as intuitive as possible for them. And if being off a week was working for some people, then being off two days should work for even more people.

So we decided to test it.

Another reason for doing the research is that some patients were stopping drugs on weekends anyway, and doctors need to know how to advise them.

So we enrolled 10 people who had virologic suppression on Sustiva (efavirenz), ten others taking Viramune (nevirapine), and 10 taking protease inhibitors, to join our study. We are now beyond a year in this study for most of those involved. We presented our 24-week findings at the Bangkok conference in the summer of 2004.

Five-On-Two-Off Study Early Results

Dr. Cohen: What we found depended on the drug regimen the patients were taking. We saw uniform success (at 24 weeks) for the people taking Sustiva; they all had undetectable viral load at that time. We are continuing to follow them and so far we are able to keep going with this research. While there have been rare blips of viral load, we have not seen virologic failure in this group.

With Viramune we had only seven people out to week 24, but those seven also remained suppressed with viral load under 50 copies. While there were occasional blips of viral load, even in rare cases to a few hundred copies, when we kept them on the five-day on two-day off they would re-suppress, at least out to week 24.

The protease inhibitors were a different story. At week 24, of the 10 people, two of them had virologic rebound, one to 1300 copies and the other to 3,000. So following our protocol we put them back on continuous treatment and got resistance testing. The good news is that neither person on the boosted protease inhibitors developed any resistance we could measure to those drugs. They were able to re-suppress on continuous treatment, so they didn't lose any ground.

Why would these drugs differ? One possible explanation is that Sustiva has a long half-life in the body. With two days off, essentially everybody still had enough of the drug in their blood to provide an adequate antiviral effect, even 48 hours after the last dose. And some of these people were also on tenofovir, which also has a long half-life.

This is very different from the protease inhibitors. Both people who had the virologic failure were on Kaletra and saquinavir (either Invirase or Fortovase). And both these drugs were below detectable levels in the blood after two days off.

The fact that drug level goes down sets the stage for rebound, but does not fully explain it. For Dybul had found that some people could maintain suppression even after a week off a protease inhibitor. While they were on boosted indinavir, it would be expected to be gone after two days off. Why could they maintain suppression when they were off effective drug for five more days every two weeks?

A possible answer is the nucleosides. It turned out that both of the people in our study who had rebounded by week 24 were not on effective nucleosides. One person was just on Kaletra and saquinavir with no nucleosides, and the other was on nucleosides but had high-level resistance to them. So it may be that at least some of the nucleosides are essential in maintaining long-term suppression after you stop the medications, in a way that is perhaps beyond half-lives. Maybe these drugs interfere with rebound after interruption in a way that we don't understand yet. Mark's studies all

include nucleosides.

Mark Dybul is now doing a randomized trial in Africa of the five-two schedule, and he mentioned interim results at the Bangkok meeting suggesting that it was working for all but one participant. It looks like many people can be off on weekends on Sustiva-based regimens and maintain suppression.

Does this mean that a five-two regimen is ready for general use in well-suppressed patients, that we know enough to recommend it? No, there might still be people who have viral rebound with as little as two days off. There may be people in whom the virus is less than 50 and not all the way suppressed, but 49 copies and ready to come roaring back. We computed a statistical confidence interval and can be reasonably confident that this works for Sustiva-based regimens, but it might still have virologic failure some percent of the time. We are not ready to recommend it outside of a research framework without more data.

Quality of Life Improvement

Dr. Cohen: Certainly this research needs to be done. We gave people on our study a quality-of-life survey. We asked if five days on and two days off mattered to them, compared to the continuous therapy they had been on. We gave them a scale of zero to 10 -- 10 meaning they strongly prefer five on two off, and five meaning they don't care one way or the other.

Essentially everybody circled 10. There was a strong preference for this schedule. Even thought it was just two days, people liked having their weekends off the medicines. That shouldn't surprise us, as people like having their weekends off in the rest of their lives as well.

So in terms of patient preference, this regimen deserves more study.

And it reduces drug costs by more than 25%. If we had a 25% price decrease for these drugs, people would be amazed at how important that was. Here we have such a decrease for some patients -- obviously important for governments and insurers. So we think that interest will be sustained, and hopefully more research will be done.

But it is not clear who will pay for the research. For obvious reasons the pharmaceutical industry has had a very cautious attitude. Though we should acknowledge and complement Boehringer Ingelheim, the only pharmaceutical we could find that was willing to support this research.

ATN: One thing to make clear to people -- how suppressed did the volunteers have to be to get into the study in the first place?

CC: Our requirement was very simple. You had to have a viral load undetectable (on an ultrasensitive assay) for at least the past 3 months. And we also required a CD4 count above 200 for three months, in this study. Because of the fragility of people with CD4 below 200, we didn't want to take the risk with them.

ATN: Where can readers find out more?

Dr. Cohen: A poster was presented at the Bangkok conference [1].

Funding: This trial was funded by The Linda Grinberg Foundation for AIDS and Immune Research (currently "Foundation for AIDS and Immune Research," now changing its name), The Campbell Foundation, and Boehringer Ingelheim (which contributed funding for the nevirapine cohort).

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abstract).

Behind "AIDS Breakthrough" Headlines, December 2004: Important Research, Not So New

by John S. James

Press stories in mid December 2004 about an AIDS breakthrough from Rutgers University and elsewhere were exaggerated in the media, but the treatment development is real and important. It concerns a family of experimental antiretrovirals called DAPYs, now in early human trials. These drugs are in the same class as efavirenz (Sustiva) and nevirapine (Viramune), but they appear to be much more effective against HIV, in large part because they have been rationally designed to make it very difficult for the virus to develop resistance against them. They are active against HIV that has become resistant to efavirenz and nevirapine.

Almost three years ago at the Retroviruses conference in early 2002 the public learned that one of these drugs, TMC125 (an experimental antiretroviral made by Tibotec) produced an almost 2-log (100 fold) drop in HIV viral load in only 1 week, in a human study in 12 volunteers. TMC125 is now in large phase II trials at many different sites. For more information about the early human report, see AIDS *Treatment News*, April 12, 2002, http://www.aids.org/atn/a-379-01.html. Twelve-week results from the phase II studies of TMC125 are expected in 2005, possibly at the Retroviruses conference in February.

A key element in the design of these drugs is the use of flexible molecules, so that they can fit into different shapes of the "active pocket" of the reverse transcriptase enzyme, even after that shape changes due to resistance mutations that could make non-flexible molecules ineffective. The two different kinds of flexibility used are sometimes called "wiggling" and "jiggling." This approach may be useful for treatment of many diseases, not just HIV.

The occasion for the December 2004 media was an upcoming publication in the *Journal of Medicinal Chemistry* about a new compound (called R278474, or rilpivirine), that works like TMC125 but might be more effective [1]; it is much earlier in testing, however. R278474 was 10 to 20 times more active than efavirenz in laboratory tests -- and no resistance breakthrough was observed at 30 days, while it was seen at six days with efavirenz. This paper describes the drug, and also the technical history of the development of DAPY drugs including TMC125 and R278474, emphasizing the work of multidisciplinary teams of scientists in Belgium and the U.S.

Longer versions of the recent news reports are at

* Newhouse News Service, http://www.newhousenews.com/archive/macpherson122004.html
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Sculptra (Formerly New Fill) for Facial Wasting -- Where to Find Information on the Patient-Assistance Program

by John S. James

Sculptra™ (marketed in some countries as

New Fill™) was approved in August 2004 by the FDA "for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus." It was approved narrowly for this use because of the great need of many patients -- but the FDA wants to see more data before allowing its wider use for cosmetic purposes, where the need is not as great.

The product is expensive in the U.S. (about three times the price in Europe) -- in addition to the cost of doctors' services, which can vary greatly. It is important to find a physician who is well trained or experienced in its use.

Dermik Laboratories (owned by Sanofi-Aventis), the company now selling Sculptra in the U.S., is setting up a patient-assistance program that will provide free or reduced-cost drug to patients who meet certain income and other eligibility requirements. It does not pay the doctors' bill, however. The key issue will be to get Sculptra covered by regular health insurance, like other reconstructive medicine. Some companies are refusing to pay for it by claiming it is "cosmetic." But many patients cannot maintain their job or career without the treatment.

Information about Sculptra -- choosing a doctor, getting coverage through one's health insurance, or getting patient assistance if insurance is not available -- is changing rapidly:

* Currently (December 2004) the best information is on an email list run by well-known activist Nelson Vergel. You can read an archive of the messages even without subscribing, at http://health.groups.yahoo.com/group/pozhealth/ Also, you can subscribe by sending a blank email to PozHealth-subscribe@yahoogroups.com -- and then following the instructions you will receive from Yahoo to confirm that you want the subscription. If you subscribe you may want to use the Digest option (to get no more than one email per day), as recently there were about 30 new messages a week on Sculptra alone. Note the medical necessity letter to help doctors in requesting reimbursement, at http://health.groups.yahoo.com/group/PozHealth/message/8047.

* The official number for both doctors and patients to call for the Sculptra Access Program is 1-888-SCULPTRA (888-728-5787). Also see the official Web site, http://www.sculptra.com/. Note the patient information sheet, but also the physician information at http://www.sculptra.com/US/resources/SculptraPI.pdf

You could also use a Google search, such as "Sculptra patient assistance" (without the quotes), or "Sculptra 2005" (also without the quotes) to locate recent articles.

A background article by Bob Roehr in the *Dallas Voice*, published December 2004 or earlier, is at http://www.dallasvoice.com/articles/dispArticle.cfm?Article_ID=4418

Warning: Do Not Combine Reyataz and Prilosec

A new study has found that if Reyataz (atazanavir), whether taken with or without ritonavir, is used with Prilosec (omeprazole, a proton-pump inhibitor used to reduce stomach acidity, for treating acid-reflux disease or other conditions), the blood level of atazanavir is reduced by three quarters or more, probably making it ineffective and leading to viral resistance. A December 2004 warning from Bristol-Meyers Squibb and the FDA said that doctors should not coadminister atazanavir (with or without ritonavir) with omeprazole. (This was already the recommendation before the new warning, but now the seriousness of the problem is more clear.)

Another kind of medicine to reduce stomach acidity, H2-receptor antagonists (such as Zantac, Tagamet, etc.) might also lower atazanavir levels; a study to find out is now ongoing. Until its results are available the following warning is included in the Reyataz label (full prescribing information

for physicians), as of December 2004:

"Reduced plasma concentrations of atazanavir are expected if H2-receptor antagonists are administered with REYATAZ (atazanavir sulfate). This may result in loss of therapeutic effect and development of resistance. To lessen the effect of H2-receptor antagonists on atazanavir exposure, it is recommended that an H2-receptor antagonist and REYATAZ be administered as far apart as possible, preferably 12 hours apart."

For more information check the current label, available at http://www.reyataz.com. See the "patient information" or "full prescribing information" links (in early January 2004 these worked with some but not all Web browsers).

Treatment Interruption: Most Patients Could Not Maintain Immune Control

by John S. James

A leading research group on HIV treatment interruption reported that very early antiretroviral treatment with supervised interruptions did not enable most patients to develop enough immune control to stop antiretrovirals permanently. While 11 of 14 patients were able to remain off treatment for as long as 90 days (with viral load under 5,000, an arbitrary level based on the treatment guidelines in use when the study started), only 3 of the 14 could stay off treatment entirely for as long as two years. Seemingly good HIV-specific immune responses were found, but often they were not protective. It is not known if the viral setpoint was lowered in these patients by this early treatment protocol. This research update appeared in the December 2004 issue of *PLOS Medicine* (a new online journal published by the Public Library of Science), where it is freely available to anyone [1].

Treatment interruption in order to establish immune control should not be confused with other kinds of treatment interruptions, such as the five-days-on-two-days-off reported elsewhere in this issue. That more modest interruption seeks to reduce antiretroviral use in carefully selected patients in order to reduce expense and improve quality of life, not to help the immune system gain permanent control of HIV. Treatment is discontinued for only two days then automatically restarted before the virus has a chance to come back -- not discontinued for years at a time if viral load stays low.

Comment

Our impression is that the early HIV treatment and interruption to help build immune control of the virus probably is helping, but not enough for most patients. Some of the newer research into HIV immunity and pathogenesis may ultimately provide the additional help necessary. We need more research on why some primate species (and a few people) do not get infected with HIV, or do get infected but then do not get sick, and whether some of the mechanisms involved could be produced artificially by drug treatment.

It will be necessary to build public-interest advocacy to make sure that needed research happens, since the companies already selling antiretrovirals may not have an incentive to greatly reduce their use.

References

1. *PLOS Medicine.* December 2004; volume 1, issue 3: number e70. Open access (no subscription needed) at http://medicine.plosjournals.org/. A search for "interruption HIV" (without the quotes) will find this and related articles in *PLOS Medicine.*

India Changes Patent Law to Meet WTO Treaty, Making New Medicines Less Available to Most Citizens, Other Countries

by John S. James

By presidential decree India changed its patent law in December 2004 to meet a January 2005 deadline to allow patents on the chemical molecules used in drugs -- not only for new drugs starting in 2005 but also for many others that were patentable after 1995 (an estimated 6,000 patent applications have already been filed for these drugs). Until now India has allowed pharmaceutical patents only on the manufacturing processes used to produce drugs, not on the end products themselves -- a system designed to encourage companies to compete in low-cost manufacturing, developing the nation's industry and making medicines widely available at low prices. Despite the great success of that system, its end was required by a World Trade Organization agreement demanding that all countries switch to European/U.S. type drug patents on the chemical entities themselves. ("least developed" countries, but not India, now have the option of extending their deadline to 2016.)

Doctors Without Borders / Medecins Sans Frontieres (MSF) and other non-governmental organizations are worried that newer AIDS and other drugs will become much more expensive, and therefore less available to patients in poor countries.

According to a widely reprinted December 30 Reuters report from India, 60,000 generic brands in 60 therapeutic areas are now available in that country -- which accounts for 1% of the money value of the pharmaceuticals sold in the world but 8% of the volume, figures reflecting the low prices [1].

Other articles reported that protests were planned throughout India before the final vote to ratify the new law. And in Washington DC a protest is planned near the Embassy of India on January 8.

An important article in *Nature Medicine*, December 30, notes that India is the fourth largest producer of pharmaceuticals in the world [some say it is the third largest], and two thirds of its exports go to developing countries. It quotes an internal Indian government report as saying that in antibiotics alone, the international intellectual property agreement (known as TRIPS, which was rammed through closed-door meetings years ago when almost nobody understood the consequences of pharmaceutical patents) will cost India's economy over $700 million each year, while creating only $57 million in profits for multinationals [2]. This article also noted that at least 15% of drugs now on the market in India, including some AIDS drugs, are likely to be withdrawn -- and that India is unlikely to survive on innovative drug development alone, as all three drugs so far licensed to multinationals have not been successful, and "the first home-grown drug is at least seven years away."

Some generic companies, especially Ranbaxy, the largest pharmaceutical company in India, are more optimistic that they can adapt to a research-based system -- or at least survive by doing low-cost work for the high-profit multinationals. But this will not help the poor who need drugs.

Comment

The Reuters story cited above quoted an unnamed pharmaceutical executive who inadvertently diagnosed the problem. "There could easily be 70 to 80 million people [in India] who can afford expensive medicines, just as they go out and buy expensive cars, branded clothes and consumer goods. That is equal to the size of a UK or a Germany." But India has a population of over 1,000,000,000 people -- meaning that the industry will be pricing new drugs for less than 10% of the population, with over 90% excluded.

Reuters also noted that the new law had provisions allowing for compulsory licensing

in case of national emergencies, or for exporting medicine to countries facing public-health emergencies. However, compulsory licensing provisions have proved very difficult to use when opposed by much better financed multinational corporations. And millions of other people will fall through the cracks because their cancer or other major disease is not deemed a public emergency.

The January 2005 trade-treaty deadline has long been well known (it was originally earlier, but was extended for some countries including India). What is surprising is that nothing has been put into place to maintain even the existing, very limited access to new medicines for the majority of the world's population that cannot pay rich-country, multinational-corporate prices -- nothing remotely equal to the scope of the problem.

The real issue for the multinationals is not the poor-country markets, which are financially small, but the poor-country examples. How will thousands of people in rich countries, especially the U.S., be persuaded to accept death from cancer and other diseases because they cannot pay the tens of thousands of dollars a year that a new generation of treatments will cost -- if companies in India could manufacture and sell the same medicines for a small fraction of the price?

There are other ways to organize and finance drug development that do not sacrifice the great majority of the world's people when they need a new medicine, so that those who do have the money can be compelled to pay. And the current system is failing badly even at the innovation, is its main selling point -- denying new treatments to everyone, not only the poor. Unless effective consensus is built, the world is headed into a catastrophe where millions of lives will be sacrificed so that a few who are already very rich and influential can hold onto current arrangements, and get a little richer.

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Africa: Children's Access to Prophylaxis May Improve After Medical Study, New WHO Recommendations

By Suzy Subways

Note: *AIDS Treatment News* published this article to provide background for activists who might want to help support the political will to make this long-delayed, lifesaving treatment available to those who need it. JSJ

On November 22, 2004, days after *The Lancet* reported that the cheap antibiotic co-trimoxazole (Septra, Bactrim, and other brand names) had dramatically reduced death in a group of Zambian children with HIV, the World Health Organization (WHO), UNAIDS and UNICEF released a statement recommending the drug for all children with HIV symptoms in poor countries [1]. But activists say the global health authorities' seemingly quick action came years -- even decades -- late, and it will take a lot more work to actually deliver the drug's lifesaving promise.

Co-trimoxazole (a combination of trimethoprim and sulfamethoxazole, sometimes called TMP/SMX) was first used to prevent AIDS-related PCP (pneumocystis pneumonia) in 1985 [2] -- (although it was standard of care for prevention of PCP in other patients with immune deficiencies long before then). It also prevents toxoplasmosis in people with AIDS [3]. Between 1987 and 1992 (before combination antiretroviral treatment), the drug cut U.S. deaths from PCP by more than half [4]. Yet today, in African countries where very few can get antiretrovirals, co-trimoxazole is still hard to come by, despite its low cost.

"We do not have good estimates of how many children are getting cotrim," says the WHO's Dr. Siobhan Crowley, "but our sense from the field is that it is not enough."

Brook Baker, a Northeastern University law professor and activist with the Health GAP (Global Access Project), says children are particularly neglected, in everything from prevention to prophylaxis to antiretroviral therapy. "Mother-to-child transmission prevention reaches only 10 percent of pregnant women in Africa at best," he says. "Follow-up for children with antiretrovirals, prophylaxis, or OI medicines is a total mess. Fifty percent of HIV-positive kids die before age 2, and yet drug companies are not investigating pediatric interventions and pediatric formulations."

Previously, WHO recommended co-trimoxazole for all newborns of women with HIV and to children with low CD4 counts or an AIDS diagnosis [5]. Worried about heavy resistance to the drug in some parts of Africa (where it is used to treat other infections like dysentery and malaria) WHO did not suggest more widespread distribution -- such as to children with some symptoms but no access to HIV testing -- until now. "Concerns that this would not be effective in areas of high resistance... do not seem to have been shown to be real given this study data," Crowley says.

Dr. Diana Gibb of the UK's Medical Research Council and her British and Zambian colleagues conducted the November *Lancet* study in an area with high bacterial resistance to the medicine. Of children taking co-trimoxazole, 28 percent died, while 42 percent who took placebo died. No allergic reactions occurred. Researchers stopped the trial early so that all children enrolled could get the successful drug [6].

For Baker, the delay in carrying out this research was more than tragic. "Twenty years into the plague, we're now looking closely at prophylaxis to protect kids," he says. "It's outrageous."

But the wait for widespread access may have just begun. Since 2001, WHO has recommended co-trimoxazole for adults with symptomatic HIV disease or below 500 CD4s, and pregnant women [5]. But the authors of an October *Lancet* study of co-trimoxazole in Uganda report that the drug is still "rarely used in Africa" -- and that Uganda is only now, because of that study, developing a co-trimoxizole policy [6].

Crowley says WHO will "strongly advocate for greater coverage of prophylactic cotrim for both adults and children," and "ensure governments hear about it." The drug is cheap -- only $10 a year per child -- and WHO advises countries to distribute it free [1, 8]. But they will also need training for health care providers, not to mention the desperate scarcity of clinics themselves. David Hoos, MD, who conducts international HIV training, technical assistance and drug procurement programs for Columbia's Mailman School of Public Health, says that lack of access to antiretrovirals has meant that Africans with HIV aren't even being brought into regular care where they could get prophylaxis for opportunistic infections.

"People need to come in every month for continuity of care," he says. "It wasn't historically a question of [co-trimoxazole] being expensive -- the facilities are much more expensive." Hoos hopes major projects like the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the President's Emergency Plan for AIDS Relief (PEPFAR) will bolster Africa's health care infrastructure.

UNICEF's Liza Barrie says her organization will work with WHO and other partners this year to support the following: adaptation of co-trimoxazole treatment guidelines; training; development of new tools to forecast the number of children who will need the drug; and procurement services through UNICEF Supply Division. But it looks like the degree of involvement international agencies pursue might depend on the kind of pressure that is put on them to take action. WHO, UNAIDS and UNICEF, for their part, urge others to act. "Greater advocacy for the use of co-trimoxazole prophylaxis in children is urgently required," their statement reads [1].

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Nevirapine Misinformation: Will It Kill?

by John S. James

On December 14 and 15 the Associated Press touched off a media firestorm with stories charging that side effects of single-dose nevirapine (to prevent mothers with HIV from infecting their babies during childbirth) had been covered up. The next day it reported on the August 2003 death of a woman in a U.S. clinical trial of continued treatment with nevirapine (not single dose), due to a rare liver failure probably caused by the drug, after an abnormal blood-test result was not noticed in time. Later the AP quoted responses -- one comparing nevirapine's distribution in Africa to the notorious Tuskegee Experiment, another charging that Africans were treated like guinea pigs. In fact there never was any evidence of a significant risk of side effects from only a single dose of nevirapine. There is a risk of HIV drug resistance, but this is well known to all AIDS doctors and experts and has never been covered up.

Every day about 1,800 babies are born with HIV, mostly to women who have no treatment options either for themselves or to prevent the infection of their child. There is no reason to doubt that single-dose nevirapine works, and could prevent about half of these infections. Because of the resistance problem, single-dose nevirapine is not the first choice -- but sometimes it is the only choice possible.

The brief media storm that still threatens the lives of thousands of children grew out of a bitter dispute between two officials of the U.S. National Institutes of Health -- Jonathan M. Fishbein, M.D., a physician with clinical-trials monitoring expertise, and his supervisor, Edmund Tramont, M.D., director of the Division of AIDS (DAIDS) at the U.S. National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH. The

falling out happened rapidly; Dr. Fishbein was hired by NIH in July of 2003, and notified in February 2004 that he would be fired. Dr. Fishbein sought whistleblower status and released documents to Congress that he said showed "scientific and professional misconduct" at NIAID. The AP published selected internal NIAID emails, memos and reports (see links to these documents below). Dr. Fishbein, still a Federal employee today (earning about $178,000 a year, according to a December 29 story in *The Washington Post*), set up a Web site, http://www.honestdoctor.org, which alleges wrongdoing by NIAID officials and provides documents that had been released elsewhere; he "did not provide non-public documents to the Associated Press," according to a statement from his attorney, Stephen M. Kohn.

The danger now is that misleading nevirapine stories published around the world will cause patients, doctors, or even governments to reject single-dose nevirapine to prevent mother-to-child HIV transmission, in cases when no other treatment is possible.

Background on Nevirapine to Prevent HIV Transmission in Childbirth

Nevirapine was approved in the U.S. in June 1996, for use in combination with other antiretrovirals for treating HIV. For this use it is taken twice a day for as long as the virus is under control.

Later, a study in Uganda from 1997 to 1999 (the HIVNET 012 clinical trial) found that a single dose of nevirapine given to the mother and a single dose to the infant reduced HIV transmission (from childbirth or breastfeeding) during the first 14 to 16 weeks of life to about half of what it was with a very short course of AZT. This study in 645 mother-infant pairs, conducted as a collaboration between researchers from Johns Hopkins University and Uganda and funded by the U.S. National Institutes of Health (NIH), was published in September 1999. It showed that HIV transmission at childbirth could be greatly reduced by a very inexpensive and easy regimen, even when the mother had little or no prenatal care. It is rightly considered one of the great successes in HIV prevention.

Nevirapine alone is not the best regimen, however. Later it was learned from the same study that even the single dose sometimes selects for resistance mutations in the mother's HIV -- a serious problem because it could make her treatment more difficult in the future. This can be prevented by treating the mother's HIV if she needs antiretroviral treatment, which of course should be done anyway -- or by using a much more difficult regimen of AZT to prevent transmission -- or by adding other drugs (usually AZT plus 3TC) to suppress the virus while the nevirapine is slowly eliminated from the body. But still today the great majority of women with HIV do not have access to any antiretroviral treatment. Single-dose nevirapine is inexpensive and easy to use -- and in some areas many women will not accept a longer course of medication, because they are afraid of the consequences if people around them learn or suspect that they have HIV.

Background on the Recent Controversy

The December 2004 controversy developed because after the Uganda study had been published, an NIH audit found that data on possible side effects had not been reported correctly by the Ugandan staff. This problem in one trial did not change the known safety of single-dose nevirapine -- which has been tested in many other clinical trials and widely used to prevent maternal transmission, without side effects. In continuous, long-term use in HIV treatment, serious or fatal side effects can occur, as with any antiretroviral. But these are rare, they can be prevented with proper medical care, and they do not happen with one dose. Aside from the HIV resistance problem, there is no evidence of any significant safety risk from a single dose of nevirapine.

NIAID hired Dr. Fishbein in July 2003, to help it correct the kinds of deficiencies that had been found in the Uganda study. A key

disagreement seems to be whether the reporting problems should invalidate the conclusion from that study that single-dose nevirapine is safe and effective for preventing maternal-infant transmission of HIV.

Links to the three AP document-release Web pages, one for each day's story, are
http://wid.ap.org/nevirapine1.html,
http://wid.ap.org/documents/nevirapine2.html, and
http://wid.ap.org/documents/nevirapine3.html.
An unsigned email from Honestdoctor.org to this writer, in response to our request for comments on an early draft of this article, specifically asked *AIDS Treatment News* to direct our readers to the documents on these pages in order to show Dr. Fishbein's side of the issue, and noted that "all the documents about 012 available on the site [http://www.honestdoctor.org] are public, many having been posted by AP last week." It is unusual for a wire-service story to link to a page set up by the wire service to release documents. If AP later takes them offline, check http://www.honestdoctor.org.

Comment

This whole dispute concerns a nevirapine trial that was completed and published over five years ago -- and recent disagreements over how to report flaws in the research that were discovered after publication. These flaws are universally acknowledged and were being addressed well before Dr. Fishbein arrived at NIH. They almost certainly do not affect our current understanding of the risks and benefits of nevirapine.

We looked through all the documents on Honestdoctor.org as of December 22, 2004, including those on the AP pages, and found nothing there that raised any new doubt on single-dose nevirapine -- now established by much more than the one trial in Uganda. Instead, the documents on that site show the extensive work that NIH and others were doing, both before and after Dr. Fishbein was hired, to correct universally acknowledged reporting problems. The goal was and is to re-analyze the Uganda trial in the light of all available information, both to re-check its conclusions when possible, and also to improve clinical research in the future, particularly in developing countries, which often have a steep learning curve in applying standards created for pharmaceutical-company research at sites with far more resources. We do not know why Dr. Fishbein alleged "widespread scientific and professional misconduct at the NIH Division of AIDS (DAIDS)" (quote from Honestdoctor.org).

The biggest public controversy concerned the rewritten safety report that was the subject of the second AP story, on December 14. (Both versions are available on the AP document-release page
http://wid.ap.org/documents/nevirapine2.html.) We do not know NIH rules and procedures, but it is our understanding that Dr. Tramont was responsible for that report, not the team as a whole. Dr. Tramont's version provided more overview, while the previous version more deeply analyzed the problems -- and was repeatedly critical of management decisions not to investigate certain problems further. Dr. Tramont's also differed in noting something the study did right:

"These health visitors [who assisted in the trial in Uganda] knew each patient individually and used culturally sensitive methods of making the contact. As a result of their efforts, maternal and infant follow-up overall for the first six weeks of the study was 97.4% for those who received ZVD [AZT] and 98% for those in the NVP [nevirapine] group. The 18 months follow-up of the study was also high, 93.8% for the ZVD group and 96.1% for the NVP group."

A separate issue, not part of the public controversy but being discussed among some activists and researchers, is whether the current U.S. FDA's GCP (Good Clinical Practice) research standards (which were required but not always followed in the nevirapine trial) are always appropriate for research in developing countries, for which they were not designed. The goal is not weaker standards, but different ways to get at least equally good data, with better patient protection than the current system

affords.

For example, simply clarifying which U.S.-government standard for adverse-event reporting should have been used when, and designing reporting forms appropriately so that dates would clearly be missing if they were stamped on the back side where they would not be faxed, and having enough blank forms so they would not be re-used to fax multiple reports, would have improved adverse-event reporting from HIVNET 012 in Uganda (see the original version of the safety review, April 3, 2003, at http://wid.ap.org/documents/nevirapine2.html). Also, according the Dr. Tramont's version (available on the same Web page), the Uganda study team consistently defined "serious" adverse events as those leading to hospitalization or death, which was the customary practice in that medical community, instead of using the more complex NIAID research definitions; the change was never formally approved by NIAID, however. Dr. Tremont's report suggested that with modifications currently accepted by the team (also counting as "serious" those problems that needed treatment to avoid hospitalization, or those that needed hospitalization though the patient refused it) the simpler definition could work.

A strong case could be made that imposing the same research requirements regardless of infrastructure and environment can result in second-class standards for developing countries, since there was little or no attempt to make the standards they must use appropriate and workable for them -- while there was such flexibility in the U.S. and other rich countries where the standards developed. Instead of fighting over how strictly to enforce rules that are sometimes unworkable, why not design rules that will better protect people and data, while helping staff get their work done correctly?

Despite the problems in this trial five years ago in Uganda, there is no reason to doubt that single-dose nevirapine works and reduces HIV transmission to about half of what it would be without treatment. (It may do better than that, since the comparison group was not a placebo but a very short course of AZT, which may have had fewer HIV transmissions than a placebo would have.) The management of NIAID's Division of AIDS, like almost all other AIDS experts, wants to focus on public-health efforts to make preventive and other treatment available, and not derail these efforts by fighting over technical problems in a trial that ended five years ago, when the medical and scientific results of that trial remain firmly established regardless. This is not "scientific and professional misconduct."

AIDS organizations including the Elizabeth Glaser Pediatric AIDS Foundations did well in answering the misinformation about nevirapine. But the damage had already been done. The news story was unexpected because it was tied to no medical or scientific development; it went around the world immediately and no answer could catch up. It is possible that children have already been born with HIV as a result, and that many more will be infected unnecessarily.

Later Dr. Fishbein told *Science* that "he is 'not in disagreement' that nevirapine saves lives. 'My issue is not nevirapine, but the process'" (December 24, 2004; see reference below).

What Can We Learn for the Future?

This is not the last time the AIDS world will face mass-media storms that carry serious misinformation throughout the world. What can we do about it?

AIDS needs a major organization dedicated to consensus development, and able to offer reporters a single entry point to learn what credible consensus exists on almost any AIDS issue. No position will speak for everybody, but the process should be open to hearing and understanding all dissenting views. Two or more incompatible consensus clusters could emerge, and they would need to be represented by different organizations. But reporters could immediately find broadly credible statements, and talk with experts about them. They might still publish misinformation, but at least an answer could go out with it -- or be clearly missing from their story.

Years ago AIDS had more influence

through policy organizations in Washington DC than it does now. Often they represented insiders with their own interests more than a national or world community; for example, treatment and international issues were mostly locked out for years, and usually the only way to have a voice was to be part of the scene in Washington, to be at the right meetings and dinners. Groups like the AIDS Action Council became trade associations, only without admitting it -- and had a deep fear of grassroots activity, and no way for non-specialists to get involved. Still they served an important purpose in providing reporters and others with a common starting point for policy discussion. We miss that today.

Now we need a new kind of organization that prides itself on listening and learning from different people (almost like social scientists exploring what is out there instead of imposing their own view) -- but then finds and suggests practical, creative ways these views and movements can work together in a larger whole. And we need funded, top-quality media outreach that reflects consensus of those working on the epidemic, is on duty at all times, and can answer misinformation immediately.

Communication Note

Ten days into this controversy Dr. Fishbein had a better Web site than most AIDS organizations do after many years -- immediately raising the communication standard. AIDS will face media attacks in the future, and must get its house in order.

Honestdoctor.org is well organized, allowing readers to see immediately what is available and navigate to what they want. The site has an extensive collection of recent press articles, consistently and attractively laid out. Under "Definitions" it has a list of acronyms, a list of people with their titles, and even organizational diagrams of NIAID and DAIDS; it will also have a glossary. When documents are photographed and displayed as images, they are processed correctly, so that they are entirely readable and yet download rapidly on any Internet connection. And last but not least this site has clearly legible type on its main pages, when most sites have at least some text that is too small, too light, or without enough contrast between text and background.

AIDS organizations should ask for volunteer or professional Web help that can do at least as well. Remember that our visitors have millions of other pages a few clicks away, and if a site is poorly organized or otherwise hard to use, many will leave.

For More Information

Here are sources for more information on the recent nevirapine controversy. Except for the last one, they are December 2004 statements or articles in chronological order.

* December 14, 2004, "Elizabeth Glaser Pediatric AIDS Foundation on issue of prevention of mother-to-child transmission of HIV/AIDS and single-dose nevirapine,"
http://www.pedaids.org/press_release_nevirapine_december_14_2004.htm

* December 15, "Boehringer Ingelheim provides key background on nevirapine,"
http://www.boehringer-ingelheim.com/corporate/asp/news/ndetail.asp?ID=2574

* December 15, "Project Inform statement regarding the use of single-dose nevirapine to prevent mother-to-child transmission of HIV,"
http://www.projectinform.org/news/04_12nvppr.html

* December 15, Treatment Action Campaign, South Africa, "Single-dose nevirapine is safe and effective: But public health facilities must switch to more effective regimens wherever possible."
http://www.tac.org.za/newsletter/2004/ns15_12_2004a.html

* December 17, the U.S. National Institute of Allergy and Infectious Diseases, "Questions and answers: The HIVNET 012 study and the safety and effectiveness of nevirapine in preventing mother-to-infant transmission of HIV,"
http://www2.niaid.nih.gov/newsroom/Releases/HIVNET012QA.htm

* December 21 *The New York Times*, "Furor

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